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Dated

13 MAY 1997

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Patents Act 1977
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10 FEB 1997

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MGH/PC/MG/P07557GB

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9702668.6

3. Full name, address and postcode of the or of each applicant (underline all surnames)

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Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

6602247001

4. Title of the invention

PORCINE RETROVIRUS

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

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547002

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Country

Priority application number
(if you know it)Date of filing
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

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- See note (d))

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Porcine Retrovirus

The present invention relates inter alia to porcine retrovirus (PoEV) fragments, in particular polynucleotide fragments encoding at least one porcine retrovirus expression product, a recombinant vector comprising at least one polynucleotide fragment, use of PoEV polynucleotide fragments in the detection of native porcine retrovirus, a host cell containing at least one PoEV polynucleotide fragment or a recombinant vector comprising at least one PoEV polynucleotide fragment, PoEV polypeptides, antibodies immuno-reactive with PoEV polypeptides, pharmaceutical compositions comprising recombinant PoEV polypeptides for use as prophylactic and/or therapeutic agents and uses of PoEV polynucleotide fragments and/or polypeptides in medicine, including veterinary medicine and in the preparation of medicaments for use in medicine, including veterinary medicine.

Porcine retrovirus (PoEV) is an endogenous (genetically acquired) retrovirus isolated from pigs and expressed in cell lines derived from porcine material. There are no known pathogenic effects associated with the virus per se in its natural host although the virus appears to be associated with lymphomas in pigs and related viruses are associated with leukaemias and lymphomas in other species. The virus has been reported to infect cells from a variety of non-porcine origins and is, therefore, designated as a xenotropic, amphotropic or polytrophic virus (Lieber MM, Sherr CJ, Benveniste RE and Todaro

that it is substantially free of biological material with which the whole genome is normally associated in vivo. The isolated polynucleotide fragment may be cloned to provide a recombinant molecule comprising the polynucleotide fragment. Thus, "polynucleotide fragment" includes double and single stranded DNA, RNA and polynucleotide sequences derived therefrom, for example, subsequences of said fragment and which are of any desirable length. Where a nucleic acid is single stranded then both a given strand and a sequence complementary thereto is within the scope of the present invention.

In general, the term "expression product" refers to both transcription and translation products of said polynucleotide fragments. When the expression product is a "polypeptide" (i.e. a chain or sequence of amino acids displaying a biological and/or immunological activity substantially similar to the biological and/or immunological activity of PoEV virion core, polymerase and/or envelope protein), it does not refer to a specific length of the product as such. Thus, the skilled addressee will appreciate that "polypeptide" encompasses inter alia peptides, polypeptides and proteins of PoEV. The polypeptide if required, can be modified in vivo and in vitro, for example by glycosylation, amidation, carboxylation, phosphorylation and/or post-translational cleavage.

Polynucleotide fragments comprising portions encompassing the PoEV genome, and derived from retrovirus particles released from a reverse transcriptase-positive porcine kidney cell line PK-15, have been molecularly cloned into a plasmid vector. This was achieved by synthesising cDNAs of PoEV RNA genomes which were

Preferred fragments of this aspect of the invention are polynucleotide fragments encoding: (a) at least one of the three polypeptides having an amino acid sequence which is shown in Figure 1; (b) encoding a polypeptide which is a physiologically active and/or immunogenic derivative of at least one of the polypeptides defined in (a); or (c) which is complementary to a polynucleotide sequence as defined above; or polynucleotide fragments: (a) comprising at least one of the ORFs shown in Figure 1 or comprising a corresponding RNA sequence; (b) comprising a sequence having substantial nucleotide sequence identity with a sequence as described in (a) above; or (c) comprising a sequence which is complementary to a sequence as described in (a) or (b) above. It is to be understood that the term "substantial sequence identity" is taken to mean at least 50% (preferably at least 75%, at least 90%, or at least 95%) sequence identity.

The polynucleotide fragment of the present invention may be used to examine the expression and/or presence of the PoEV virus in donor animals and cells, tissues or organs derived from the donor animals to see if they are suitable for xenotransplantation (i.e. PoEV free). In addition, the recipients of pig cells, tissues or organs can be examined for the presence and/or expression of PoEV virus directly or by co-culture or infection of susceptible detector cells.

A polynucleotide fragment of the present invention may be used to identify polynucleotide sequences within the PoEV genome which are PoEV specific (i.e. it is not necessary for the complete PoEV genome to be identified). Such PoEV specific

there may be less than 10, preferably less than 5 mismatches). Thus, the present invention also provides anti-sense or complementary nucleotide sequence(s) which is/are capable of specifically hybridising to the disclosed DNA sequence. If a PoEV specific polynucleotide is to be used as a primer in PCR and/or sequencing studies, the polynucleotide must be capable of hybridising to PoEV nucleic acid and capable of initiating chain extension from 3' end of the polynucleotide, but not able to correctly initiate chain extension from non PoEV sequences (especially from human, or non-PoEV porcine sequences).

If a PoEV specific test polynucleotide sequence is to be used in hybridisation studies, to test for the presence of PoEV nucleic acid in a sample, the test polynucleotide should preferably remain hybridised to a sample polynucleotide under stringent conditions. If desired, either the test or sample polynucleotide may be immobilised. Generally the test polynucleotide sequence is at least 10 or at least 50 bases in length. It may be labelled by suitable techniques known in the art. Preferably the test polynucleotide sequence is at least 200 bases in length and may even be several kilobases in length. Thus, either a denatured sample or test sequence can be first bound to a support. Hybridization can be effected at a temperature of between 50 and 70°C in double strength SSC (2xNaCl 17.5g/l and sodium citrate (SC) at 8.8g/l) buffered saline containing 0.1% sodium dodecyl sulphate (SDS). This can be followed by rinsing of the support at the same temperature but with a buffer having a reduced SSC concentration. Depending upon the degree of stringency required, and thus the degree of

therein or an RNA equivalent, or with a part of such a strand. Preferably such a part is at least 10, at least 30, at least 50 or at least 200 bases long. It may be an ORF or a part thereof.

Oligonucleotides which are generally greater than 30 bases in length should preferably remain hybridised to a sample polynucleotide under one or more of the stringent conditions mentioned above. Oligonucleotides which are generally less than 30 bases in length should also preferably remain hybridised to a sample polynucleotide but under different conditions of high stringency. Typically the melting temperature of an oligonucleotide less than 30 bases may be calculated according to the formula of; 2°C for every A or T, plus 4°C for every G or C, minus 5°C . Hybridisation may take place at or around the calculated melting temperature for any particular oligonucleotide, in $6 \times \text{SSC}$ and 1% SDS. Non specifically hybridised oligonucleotides may then be removed by stringent washing, for example in $3 \times \text{SSC}$ and 0.1% SDS at the same temperature. Only substantially similar matched sequences remain hybridised i.e. said oligonucleotide and corresponding PoEV nucleic acid.

When oligonucleotides of generally less than 30 bases in length are used in sequencing and/or PCR studies, the melting temperature may be calculated in the same manner as described above. The oligonucleotide may then be allowed to anneal or hybridise at a temperature around the oligonucleotides calculated melting temperature. In the case of PCR studies the annealing temperature should be around the lower of the calculated melting temperatures for the two priming oligonucleotides. It is to be

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(i.e. hybridisation studies) for detecting the presence or otherwise of PoEV polynucleotide in the nucleic acid of pigs or in cell, tissue or organ samples taken from pigs (e.g. from potential transplant organs such as liver, kidney and heart). Such cells, tissues or organs can be derived from transgenic animals produced as described in EP-A-0493852, or by other means known in the art. Thus the cells, tissues or organs of transgenic pigs can be associated with one or more homologous complement restriction factors active in humans to prevent/reduce activation of complement.

Furthermore the polynucleotide fragments of the present invention can be used to analyze the genetic organisation of endogenous PoEV located in the animal cell genome in pigs thus permitting the screening of herds of pigs for altered provirus and genomic loci (e.g. non-expressed provirus loci). Such a screening method would facilitate, for example, screening in a population of animals which are bred to lack expressed provirus and genomic loci and/or loci that do not encode infectious virus particles.

Reagents may also be developed from said polynucleotide fragments as aids to develop pigs that do not express an infectious, PoEV capable of infecting humans. Such pigs could still contain partial defective genomes that could result in the expression of non-infectious particles, viral proteins or viral mRNA. Alternatively, it may be possible to use constructs derived from the PoEV polynucleotide sequence to act as insertional mutagens to knockout the productive infectious PoEV in embryos, embryonic stem cells, or cells containing

taken up by cells and the polynucleotide fragment of interest expressed, producing protein. Presentation of the protein on cell surface stimulates the host immune system to produce antibodies immunoreactive with said protein as part of a defence mechanism. Thus, expressed protein may be used as a vaccine.

Inactivated vaccines can be produced from PoEV's or cells releasing PoEV. Such infected cells may be generated by natural infection or by transfection of a proviral clone of PoEV. It will be understood that a proviral clone is a molecular clone encoding on at least one antigenic polypeptide of PoEV. After harvesting the virus and/or the infected cells, viruses or infected cells present can be inactivated for example, with formaldehyde, glutaraldehyde, acetyleneimine or other suitable agent or process to generate an inactivated vaccine using methods commonly employed in the art. (CVMP Working Party on Immunological Veterinary Medicinal Products (1993). General requirements for the production and control of inactivated mammalian bacterial and viral vaccines for veterinary use). Subunit vaccines may be prepared from the individual proteins encoded by the gag, pol and env genes. Typically a vaccine would contain env gene products either alone or in combination with gag genes produced by expression in bacteria, yeast or mammalian cell systems.

Proviral clones of PoEV can be engineered to develop single cycle or replication defective viral vectors suitable for vaccination using techniques. Such viral vectors known in the art (e.g. MuLV Murine Leukaemia Retrovirus, Adenovirus and Herpesviruses (Anderson WF. (1992). Human Gene Therapy. *Science*

the pig family). These variations may be demonstrated by (an) amino acid difference(s) in the overall sequence or by deletions, substitutions, insertions, inversions or additions of (an) amino acid(s) in said sequence. All such derivatives showing active polymerase and/or envelope polypeptide physiological and/or immunological activity are included within the scope of the invention. For example, for the purpose of the present invention conservative replacements may be made between amino acids within the following groups:

- (I) Alanine, serine, threonine;
- (II) Glutamic acid and aspartic acid;
- (III) Arginine and leucine;
- (IV) Asparagine and glutamine;
- (V) Isoleucine, leucine and valine;
- (VI) Phenylalanine, tyrosine and tryptophan

Moreover, recombinant DNA technology may be used to prepare nucleic acid sequences encoding the various derivatives outlined above.

As is well known in the art, the degeneracy of the genetic code permits substitution of bases in a codon resulting in a different codon which is still capable of coding for the same amino acid, e.g. the codon for amino acid glutamic acid is both GAT and GAA. Consequently, it is clear that for the expression of polypeptides with the amino acid sequences shown in Figure 1 or fragments thereof, use can be made of a derivative nucleic acid sequence with such an alternative codon composition different from the nucleic acid sequence shown in said Figure 1.

Furthermore, fragments derived from the PoEV polymerase

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sequences according to the invention are known in the art (e.g. Rodriguez, R.L. and Denhardt, D.T., Edit., Vectors: a survey of molecular cloning vectors and their uses, Butterworths, 1988).

The methods to be used for the construction of a recombinant nucleic acid molecule according to the invention are known to those of ordinary skill in the art and are inter alia set forth in Sambrook, et al. (Molecular Cloning: a laboratory manual Cold Spring Harbour Laboratory, 1989).

The present invention also relates to a transformed cell containing the PoEV polynucleotide fragment in an expressible form. "Transformation", as used herein, refers to the introduction of a heterologous polynucleotide fragment into a host cell. The method used may be any known in the art, for example, direct uptake, transfection or transduction (Current Protocols in Molecular Biology, 1995. John Wiley and Sons Inc). The heterologous polynucleotide fragment may be maintained through autonomous replication or alternatively, may be integrated into the host genome. The recombinant nucleic acid molecules preferably are provided with appropriate control sequences compatible with the designated host which can regulate the expression of the inserted polynucleotide fragment, e.g. tetracycline responsive promoter, thymidine kinase promoter, SV-40 promoter and the like.

Suitable hosts for the expression of recombinant nucleic acid molecules may be prokaryotic or eukaryotic in origin. Hosts suitable for the expression of recombinant nucleic acid molecules may be selected from bacteria, yeast, insect cells and mammalian cells.

NaCl, 1mM EDTA) and the virions disrupted by the addition of 1ml of lysis/binding buffer. Dynabeads Oligo(dT)₂₅ were conditioned according to the manufacturer's instructions and added to the virus disrupted solution. Viral RNA is allowed to bind to the Dynabead for 10 minutes before the supernatant is removed and the bound RNA was washed three times with washing buffer with LIDS (0.5ml) and twice with washing buffer alone. The RNA is finally resuspended in 25 µl of elution solution. All procedures were performed at ambient temperature. RNase contamination was avoided by the wearing of gloves, observation of sterile technique and treatment of solutions and non-disposable glass and plasticware with diethyl pyrocarbonate (DEPC). The RNA was resuspended in DEPC- treated sterile water.

Example 2

Synthesis of cDNA

cDNA was synthesised from the purified genomic RNA using Great Lengths™ cDNA amplification reverse transcriptase reagents (Clontech Laboratories Inc.) following the manufacturer's instructions. The RNA was primed with both oligo(dT) and random hexamers to maximise synthesis.

The Great Lengths cDNA synthesis protocol is based on a modified Gubler and Hoffman (1989) protocol for generating complementary DNA libraries and essentially consists of first-strand synthesis, second strand synthesis, adaptor ligation, and size fractionation.

First strand synthesis: lock-docking primers anneal to the

Example 3**Molecular cloning of cDNA**

The size fractionated fragment was ligated with EcoR I- digested pZERO™ -1 plasmid vector DNA (Invitrogen Corporation, San Diego, U.S.). The ligation mix was used to transform competent TOP10F' cells and these were plated onto L-Agar containing zeocin following the manufacturer's instructions (Zero Background™ cloning kit - Invitrogen). Several of the resulting zeocin resistant colonies were amplified in L-Broth containing zeocin and the plasmid DNA was purified by alkaline lysis (Maniatis et al., 1982).

The plasmid DNA was digested to completion with the endonuclease EcoR I and the resulting DNA fragments were separated by electrophoresis through an 1.0% agarose gel (Maniatis et al., 1982), in order to check that a fragment in the predicted size fractionated size range had been cloned. A clone identified as pPoEV was used in further experimentation.

Example 4**DNA sequence analysis.**

pPoEV plasmid DNA was purified according to common techniques (Sambrook et al, 1989) and sequenced using an ABI automated sequencer. Overlapping sequencing primers from both strands of the molecular clone were used to determine the nucleotide sequence. Homologies were observed between pPoEV and the majority of retroviruses determined by using algorithms from DNASTAR Inc. Lasergene software (DNASTAR). The homologies were closest with

15 minutes. The process was repeated one further time. The sample was mixed with 5ml (3x volume) of extraction buffer (Maniatis et al., 1982).

Purification

The samples (i.e. cultured cells, porcine tissue or porcine blood cells) in proteinase K-extraction buffer containing 20µg/ml RNase and 100µg/ml proteinase K were digested for approximately 24 hours at 37°C. The deproteinised DNA was extracted twice with phenol and twice with phenol chloroform and finally precipitated by ethanol in the presence of ammonium acetate. The DNA was recovered by centrifugation at 3000g for 30 minutes and the supernatant discarded (Maniatis et al., 1982). The pellet was washed in 70% ethanol and allowed to air dry for approximately 1 hour. The DNA was allowed to re-dissolve in Tris EDTA (TE) buffer and the purity and concentration of the DNA was assessed by spectrophotometry (Maniatis et al., 1982).

Example 6

Southern blot analysis of porcine tissue and cells

In order to demonstrate that the molecularly cloned DNA comprising the insert from PoEV was derived from the PK-15 cell line (American Type Culture Collection CCL33), the DNA was hybridised against cellular DNAs and its ability to detect proviral DNA was examined.

DNA purified from pPoEV was radioactively labelled and used to probe a Southern blot of endonuclease digested DNAs derived from PK-15 cells .

Culture Collection CRL 1746) and primary porcine kidney cells (Central Veterinary Laboratory batch C04495) but not in hamster CHOK1 (American Type Culture Collection CCL61) or murine NSO myeloma cells (European Collection of Animal Cell Cultures 85110503).

In order to demonstrate that the molecularly cloned DNA comprising the insert from pPoEV could detect sequences in porcine cells and tissues in addition to PK-15 the pPoEV DNA was hybridised against cellular DNA from tissues derived from pigs and its ability to detect proviral DNA was examined (Maniatis et al., 1982).

The DNA purified from pPoEV was radioactively labelled and used to probe a Southern blot of endonuclease digested DNAs derived from pig organs including liver, kidney, heart and blood.

The DNAs probed were as follows :

- a) Copy number controls of pPoEV DNA linearized by digestion with EcoRI. One copy per haploid cell genome was estimated to be 6.84pg. The control was present at an estimated copy number of 5, 10, 20 and 50 copies.
- b) DNA purified from the porcine tissues digested with EcoRI.

A hybridisation signal was observed in all the porcine DNAs.

On completion of the amplification, 10 μ l of the reaction mixture wasrophoresed through a 5 per cent acrylamide gel. The DNA was visualised by staining with ethidium bromide and exposure to ultraviolet light (320nm).

The PCR reaction amplified a sequence of approximately 787bp from pPoEV and from porcine cells as expected indicating that the assay detected the PoEV proviral DNA. There was no specific amplification of the expected sequence in cells of non-porcine origin and therefore, the PCR reaction and recombinant clone can be used as a specific and sensitive diagnostic tool for detection of PoEV.

Example 8

Production of PoEV polypeptide in *Escherichia coli*.

The open reading frame (ORF) encoding the pol peptide was isolated from the pPoEV clone and molecularly cloned into the plasmid pGEX-4T-1 (Pharmacia Ltd.) for expression.

Two ml cultures of *E. coli* transformed with various expression constructs were grown with shaking at 37°C to late log phase (O.D._{600nm} of 0.6) and induced by the addition of IPTG to 0.1 mM. Induced cultures were then incubated for a further 2 hours after which the bacteria were collected by centrifugation. The bacterial pellet was lysed by boiling in SDS-PAGE sample buffer and the protein profile of the induced bacteria was analysed on a 12% acrylamide gel (Laemmli, 1970) followed by staining with coomassie brilliant blue dye.

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- (a) at least one of the three polypeptides having an amino acid sequence which is shown in Figure 1;
 - (b) encoding a polypeptide which is a physiologically active and/or immunogenic derivative of at least one of the polypeptides defined in (a); or
 - (c) which is complementary to a polynucleotide sequence as defined in (a) or (b).
5. As isolated polynucleotide fragment according to any one of claims 1 to 4;
- (a) comprising at least one of the ORFs shown in Figure 1 or comprising a corresponding RNA sequence;
 - (b) comprising a sequence having substantial nucleotide sequence identity with a sequence as described in (a) above; or
 - (c) comprising a sequence which is complementary to a sequence as described in (a) or (b) above.
6. A recombinant nucleic acid molecule comprising a polynucleotide fragment according to any one of claims 1 to 5.
7. A recombinant nucleic acid molecule according to claim 6 wherein the recombinant nucleic acid molecule comprises regulatory control sequences operably linked to said polynucleotide fragment for controlling expression of said polynucleotide fragment.

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17. A probe or a primer according to claim 15 or 16 which has substantial nucleotide sequence identity with a strand of the molecule depicted in Figure 1, or a strand complementary therewith, with a corresponding RNA molecule, or with a part of such a molecule.
18. A PoEV detection kit comprising a polynucleotide primer or probe according to any of claims 15 to 17.
19. Use of a PoEV specific polynucleotide in the detection of PoEV in a sample.
20. Use of a PoEV specific polynucleotide in a PCR for the detection of PoEV in a sample.
21. A pig modified so as to not express an infectious PoEV capable of infecting humans.
22. Cells, tissues or organs obtainable from a pig encoding to claim 21.
23. Use of a recombinant PoEV polypeptide according to either of claims 11 or 12 in the preparation of a vaccine.
24. Use of a polynucleotide primer or probe according to any of claims 15 to 17 in the preparation of a detection kit capable of detecting the presence of PoEV nucleic acid in a sample.

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ABSTRACTPORCINE RETROVIRUS

The present invention provides porcine retrovirus (PoEV) polynucleotide fragments, particularly those encoding at least one PoEV expression product, a recombinant vector comprising such a polynucleotide fragment or fragments, use of PoEV polynucleotide fragments in the detection of native PoEV, a host cell containing at least one PoEV polynucleotide fragment or recombinant vector, PoEV polypeptides, antibodies immuno-reactive with PoEV polypeptides, pharmaceutical compositions comprising recombinant PoEV polypeptides for use as prophylactic and/or therapeutic agents and uses of PoEV polynucleotide fragments and/or polypeptides in medicine, including veterinary medicine and in the preparation of medicaments for use in medicine.

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Figure 1

1	TGTGGGCCCCAGCGCGCTTGG	MAAAAATCCTCTTGGCTGTTTGCATCAATACCGCTTCT	60
91	CGTGAGTGTATTGGGGTGTCC	TCCTCCAGCCCGGACGACCGCGATTGCTCTTTTACT	120
121	GGCCTTTCAATTTGGTSCGTTT	ACGGAAATCCTGGGACCCACCCCTTACAACCGAGAACC	180
191	GACTTGGAGCTAAAGGATCC	TTTGGACCGTGTGTGTGTGTGGCGCGCGTCTCTGTT	240
241	CTGAGTGTCTGTTTTTCGGTGA	TCGCGCTTTTCGGTITTCAGCTGTCTCTCAGACCGTAA	300
301	GGACTGGAGGACTGTGATCAG	ACCTCTTAGGAGGATCACAGGCTGCCACCTCGGGG	360
381	ACGCCCCGGGAGGTGGGGAGA	ACAGGGACGCTCGTGGTCTCCTACTGTGGTACAGAGG	420
421	AACGAGTTCGTGTGTGAAGC	AAAGCTTCCCCCTCCGCGGCCCTCCGACCTTTTGGCT	480
481	GCTTGTGGAAGACCGCGACGG	TCGGTGTGTCTGGATCTGTGGTTTCTTCTCTGTGTG	540
541	TCCTTGTCTTGTGCGTCTTTC	TACAGTTTATAATATGGSACAGACCTGCTACCCCCC	600
		MetGlyGlnThrValThrThrProL	
601	TTAGTTTGACTCTCGACUATT	ACTGAGTTTAGATCCAGCGCTCATTAATTGTGACTTC	660
	euSerLeuThrLeuAspHis	ThrGluValArgSerArgAlaHisAsnLeuSerValG	
661	AGGTTAAGAAGGGACCTTCCG	ACTTTTGTGCTCTGAAATGGCCAACATCCGATGTTG	720
	TrValLysLysGlyProTrpG	ThrPheCysAlaSerGluTrpProThrPheAspValG	
721	GATGCCCATCAGAGGGGACCT	AAATTCAGAAATTATCCTGCGCTGTTAAGGCAATCATT	780
	lyTrpProSerGluGlyThrP	AsnSerGluIleIleLeuAlaValLysAlaIleIleP	
781	TTGAGACTGGACCCGGCTCTC	CTGATCAGGAGCCCTAATACCTTACCTGGCAAGATT	840
	heGlnThrGlyProGlySerP	ProAspGlnGluProTyrIleLeuThrTrpGlnAspL	
841	TGGCAGAAGATCCTCCGCCAT	GTAAACCATGGCTAAATAAACCAAGATAGCCAGGTC	900
	aaAlaGluAspProProPro	ValIysProTrpLeuAsnLysProArgLysProGlyP	
901	CCCGAATCCTGGCTCTTGGAG	AAAAACAAACACTCGGCCGAAAAAGTCAGCCCTCTT	960
	coArgIleLeuAlaLeuGlyS	CysAsnLysHisSerAlaGluLysValIleProSerS	
961	CCTCGTATCTACCCGAGATC	TCGAGCCGCCSACTTGGCCCGGAACCCCACTCTTTC	1020

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erSerTyrLeuProArgAsp GlyAlaAlaAspLeuAlaGlyThrProSerCysSerP

1020 CCACCCCTTATCCAGCACAC TGGTCTGAGGGGAGGCTCTCCCTCTCTGAGCTCCG 1080
 roThrProLeuSerSerThrC CysCysGluGlyThrSerAlaProProGlyAlaProV

1081 TGGTGGAGGGACCTGCTGCCA TACTCGGAGCCGGAGAGGCGCCACCCCGAAGCGACAG 1140
 alValGluGlyProAlaAlaC ThrArgSerArgArgGlyAlaThrProGluArgThrA

1141 ACGAGATCGCGATATTACCGC GCGACCTATGGCCCTCCCATGCCAGGGGGCCAAATGCG 1200
 spGluIleAlaIleLeuProI ArgThrTyrGlyProProMetProGlyGlyGluLeuG

1201 ACCCCCTCCAGTATGGCCCA TCTTCTGCAGATCTCTATAATTGGAACTAAACCATC 1260
 InProLeuGlnTyrTrpProF SerSerAlaAspLeuTyrAsnTrpLysThrAsnHisP

1261 CCCCTTTCTCGGAGGATCCCG GCGCTTCAGGGGGTTGGTGGAGTCCCTTATGTTCTCTC 1320
 roProPheSerGluAspProF ArgLeuThrGlyLeuValGluSerLeuMetPheSerH

1321 ACCAGCCTACTTGGGATGATT CAACAGCTGCTGCAGACACTCTTCAGAACCGAGGAGC 1380
 IsGlnProThrTrpAspAspC GlnGlnLeuLeuGlnThrLeuPheThrThrGlnGluA

1381 GAGAGAGAATTCTGTAGAGC TACAAATATGTTCTTGGGGCCGACCGCGACCCACGC 1440
 rgGluArgIleLeuLeuGluA ArgLysAsnValProGlyAlaAspGlyArgProThrC

1441 AGTTGCAAAATGAGATTGACA CGATTTCCTTGACTCGCTCCCGTTGGTACTACAAACA 1500
 LeLeuGlnAsnGluIleAspC GlyPheProLeuThrArgProGlyTrpAspTyrAsnT

1501 CGGCTGAAGGTAGGGGAGGCT GAAATCTATCGCCAGGCTCTCGTGGCGTCTCCCGGG 1560
 heAlaGluGlyArgGluSerL LysIleTyrArgGlnAlaLeuValAlaIlyLeuArgG

1561 GCGCCTCAGACCGGCCACTTA TTGCTTAAGGTAAGAGAGGTGATGCAGTACCGAAGC 1620
 lyAlaSerArgArgProThra LeuAlaLysValArgGluValMetGlnIlyProAsnG

1621 AACCTCCCTCGGTATTTCTTC AGSCTCATGGAAGCCTTCAGCGGGTTCCTCCCTTTTC 1680
 LuProProSerValPheLeuG ArgLeuMetGluAlaPheArgArgPheThrProPheA

1681 ATGCTACCTCAGAGGCCACAG TCCCTCAATTGGGCTTGGCTTCATTGGGAGTCCGCTC 1740
 spProThrSerGluAlaGlnL AlaSerValAlaLeuAlaPheIleGlyIleSerAlaL

1741 TCGATATCAGGAAGAACTTC TGACTTAAAGGTTACAGGAGGCTGAGTACCTTGATC 1800
 cuAspIleArgLysLysheL ArgLeuGluGlyLeuGlnGluAlaGluIleArgAspL

1801 TAGTGAGAGAGGCACAGAGCG TATTACAGAAGCGAGACACAGAGGAGAGCAACAGA 1860
 cuValArgGluAlaGlnLysV TyrTyrArgArgGluThrGluGlnGluLysGluGlnA

1861 GAAVAGAAAGGAGACAGAAAG AGGAGGAAAGACGTGATAGCGGCAATGTAAGAATT 1920
 roLysGluLysGlnArgGluC ArgGlnGlnArgArgAspArgArgGlnIleLysAsnL

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1921 TGACTAAGATCTTTGGCCGCAG GTTGAAAGGGAACAGCAGCAGGGAGAGAGAGAGATT 1930
euThrIysIleIleuAluAlu ValGlnGlyLysSerSerArgGlnArgPheArgAspP

1981 TTAGGAAAATTAGGTCTAGGGC ACACASTCAGGGAACCTGGCCATATGGACCCCACTCG 2040
heArgLysIleArgSerGly ArgGlnSerGlyAsnLeuGlyAspArgPheProLeuA

2041 ACAAGGACCAGTGTCTCTATT TAAAGAAAAGGACACTGGGCAAGGAC TCCCTCAGA 2100
SplLysAspGlnCysAlaTyr LysGlnLysGlyHisTrpAlaArgAsnLysProLysAl

2101 AGGGAAACAAAGGACCGAAGT TAGCTCTAGAAGAAGATAAAGATTAGGTGAGACGGGT 2160
ysGlyAsnLysGlyProLysP End ArgLeuGlnGlnThrGly

2161 TCGGACCCCTCCCGAGCCG CCGTAACTTTGAAGGTGGAGGGGCAACCACTTGAAGTTC 2220
SerAspProLeuProGluProArgValThrLeuLysValGluGlyGlnProValGluPhe

2221 CTGGTTGATACCGGAGUGGAG TTCACTCTCTGCTACAACCATTAGGAAACTAAAGAA 2280
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2281 AAAAAATCCTGGGTGATGGGT TACACAGGCAACGGGCACTATCCATGGAC TACCCGAGA 2340
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2341 ACCGTTGACTTGGGAGTGGGA CGTAAAGCCACTCGTTTCTGGTCACTCCCTGAGTGGCCCA 2400
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2401 GTACCCCTTCTAGGTAGAGAC TACTCACCAGATGGGAGCTCAATTTCTTTTGAACAA 2460
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2461 GGAAGACCAGAAGTGTCTGTG TAACAAACCCATCAGTGTGTTGACCTTCAATTAGAT 2520
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2521 GATGAATATCGACTATATTCT CCAAGTAAAGCCTGATCAGATATACATTCCTTGSTTG 2580
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2581 GAGCAGTTTCCCAAGCCTGG AGAAGCCGCGAGGATCGGTTTGGCAPPACAGATTCCC 2640
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2641 CCACAGGTTATTCAACTGAGG TAGTGTACACCACTATCACTCAGACATACCCCTTG 2700
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2701 AGTAGACAGGCTCGAGAGGA TTGGCCATATTTCAAAGATTAAATCCAAACAGGCGATC 2760
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2761 CTAGTTCTGTGCAATCCCTT TAATATCCCTGCTACCGGTAGGAACTCTCGGACC 2820
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2821 AATGATTATCGACCGATACAT TTGACAGAGGTCATTAAGGCTGCAACACATACAC 2880

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2941 ACAGTATTGGACTTAAAAGATGCCCTTCTTCTGCGCTGAGATTACACCCCACTAGCCAAUCCA 3000
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3001 CTTTTTGCCCTTCGAATGGAGAGATCCAGGTACGGGAAGAACCAGGCAGCTCACCTGGACC 3060
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3061 CGACTGCCCCAAGGGTTCAAGAACTCCCGACCATCTTTGACGAAGCCCTACACAGGGAC 3120
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3121 CTGGCCAACCTTCAGGATCCAACACCCCTCAGGTGACCCCTCCTCCAGTACGTGGATGACCTG 3180
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3181 CTTCTGGCGGGAGCCACCAACAGGACTCCTTAGAAGGTACGAAGGCACCTACTGCTGGAA 3240
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3241 TTGTCTGACCTAGGCTACAGAGCCCTCTGCTAAGAAGGCCAGATTTGCAGGAGAGAGGTA 3300
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3421 GCTGGATTTTGCAGACTGTGGATCCCGGGGTTTGCGACCTTAGCAGCCCCACTCTACCCG 3480
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3541 ATCAAAAAGGCCCTGCTGAGCGCACCTGCTCTGGCCCTCCCTGACGTAACTAAACCCCTT 3600
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3661 CCATGGAGGAGACCTGTGTGCTTACCTGTCAAAGAAGCTTGATCCTGTAGCCAGTGCTGG 3720
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3721 CCCGTATGCTGAAGGCTATGCGCAGCTGTGGCCATACTGGTCAAGGACGCTGACAAATTG 3780
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3901 GACAGGGTCACTTTCGCTCCACCAGCCGCTCTCAACCCTGCCACTCTTCTGCCCTGAAGAG 3960
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4141 ATCTGGGCCAGCAGCCTGCCGGAAGGAACCTCAGCGCAAAGGCTGAGCTCATGGCCCTC 4200
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4201 ACGCAAGCTTTCGGGCTGGCCGAAGGGAAATCCATAAACATTTATACGGACAGCAGGTAT 4260
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4621 TATGGGAAGGAAATCTTCCCAACAAAGAAGGGTTAGAATATGTCCAACAGATACATCGT 4680
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4681 CTAACCCACCTAGGAACCTAACACCTGCAGCAGTGGTCAGAACATCCCCCTATCATGTT 4740

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6361 GCCACCGCATAACTTGCCGGTGCCCCAATTAACTCGCTGCGGCTGACATAACACAGCC 6420
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6541	CTCCACCGACCCCTGATGCCACTTCTTCTTGTTGGCTTTGTCTATCCTCAGGGCCCTCCTTA nSerThrAspProAspAlaThrSerSerCysTrpLeuCysLeuSerSerGlyProProTy	6600
6601	TTATGAGGGGATGGCTAAAGAAAGAAAATTCAATGTGACCAAAGAGCATAGAAATCAATG rTyrGluGlyMetAlaLysGluArgLysPheAsnValThrLysGluHisArgAsnGlnCy	6660
6661	TACATGGGGGTCCCGAAATAAGCTTACCCTCACTGAAGTTTCCGGGAAGGGGACATGCAT sThrTrpGlySerArgAsnLysLeuThrLeuThrGluValSerGlyLysGlyThrCysTi	6720
6721	AGGAAAAGCTCCCCCATCCCAACACACCTTTGCTATAGTACTGTGGTTTATGAGCAGGC eGlyLysAlaProProSerHisGlnHisLeuCysTyrSerThrValValTyrGluGlnAl	6780
6781	CTCAGAAAATCAGTATTTAGTACCTGGTTATAACAGGTGGTGGUCATGCAATACTGGGTT aSerGluAsnGlnTyrLeuValProGlyTyrAsnArgTrpTrpAlaCysAsnThrGlyLe	6840
6841	AACCCCTGTGTTTCCACCTCAGTCTTCAACCAATCCAAAGATTTCTGTGTCATGGTCCA uThrProCysValSerThrSerValPheAsnGlnSerLysAspPheCysValMetValGl	6900
6901	AATCGTCCCCGAGTGTACTACCATCCTGAGGAAGTGGTCCTTGATGAATATGACTATCG nIleValProArgValTyrTyrHisProGluGluValValLeuAspGluTyrAspTyrAr	6960
6961	GTATAACCGACCAAAAAGAGAACCCGATCCCTTACCCTAGCTGTAAATGCTCGGAATAGG gTyrAsnArgProLysArgGluProValSerLeuThrLeuAlaValMetLeuGlyLeuGl	7020
7021	GACGGCCGTGGCGTAGGAACAGGGACAGCTGCCCTGATCACAGGACCACAGCAGTAGA yThrAlaValGlyValGlyThrGlyThrAlaAlaLeuIleThrGlyProGlnGlnLeuGl	7080
7081	GAAAGGACTTGGTGAGCTACATCGGGCCATGACAGAAGATCTCCGAGCCTTAAAGGAGTC rLysGlyLeuGlyGluLeuHisAlaAlaMetThrGluAspLeuArgAlaLeuLysGluSe	7140
7141	TGTTAGCAACCTAGAACAGTCCCTGACTTCTTTGTCTGAAGTGGTTCTACAGAACCGGAG rValSerAsnLeuGluGluSerLeuThrSerLeuSerGluValValLeuGlnAsnArgAr	7200
7201	GGGATTAGATCTGCTGTTTCTAAGACAAGGTGGGTATGTGCAGCCTTAAAGAGAAGATG gGlyLeuAspLeuLeuPheLeuArgGluGlyGlyLeuCysAlaAlaLeuLysGluGlnCy	7260
7261	TTGCTTCTATGTAGATCACTCAGGAGCCATCAGAGACTCCATGAACAAGCTTAGAAAAAA sCysPheTyrValAspHisSerGlyAlaIleArgAspSerMetAsnLysLeuArgLysLy	7320
7321	GTTAGAGAGGCGTCGAAGGGAAAGAGAGGCTGACCAGGGGTGGTTTGAAGGATGGTTCA sLeuGluArgArgArgArgGlnArgGlnAlaAspGlnGlyTrpPheGluGlyTrpPheAs	7380
7381	CAGGTCTCCTTGGATGACCACCCCTGCTTTCTGCTCTGACGGGGCCCTAGTAGTCTGCT uArgSerProTrpMetThrThrLeuLeuSerAlaLeuThrGlyProLeuValValLeuLe	7440

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